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Learning and Circadian Behavior

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Why was it such a surprise, that *Nature* paper in 1996, where Amir and Stewart demonstrated phase resetting by a conditioned stimulus? Did it bridge a wide gap to another discipline? Surely not; learning has long been on our plate. Or was it the unexpected nature of the unconditioned stimulus (US)? We are used to US as a traditional reinforcer that elicit specific emotional sensations, as agents inflicting pain, or satisfying hunger or thirst. But light? True, some visual images may act as reinforcers, because they somehow reach centers in the brain involved in emotional evaluation of external and internal status. But nonvisual, circadian photoreception, doing something so basic to an endogenous oscillator deep down in the hypothalamus that even plants and bacteria have evolved essentially the same response? A response as ancient and as basic to the organization of life on our rotating planet as mitosis and meiosis?

But then, why not? Reinforcers act as US (no prior experience needed) in that they signal a change in individual fitness—fitness in the Darwinian sense of expected propagation of genes into the next generation. A food reward signals an improvement in condition—that improvement may eventually lead to a slight increase in the probability of surviving and reproducing. The adequate, fitness-enhancing response is to seek situations predicting the positive reinforcement. Pain, a negative reinforcer, signals danger—danger of damage or predation, a slight (or even a terminal) decrease in reproductive value. The fitness-enhancing response is to avoid situations leading to pain. Any conditioned stimulus that can predict the US also predicts the associated change in fitness. To a nocturnal burrowing mammal, light means danger—think, for instance, of retinal UV damage or of a visual predator. The adequate responses to light are manifold. There may be an immediate (masking) response: retreat into darkness or suppression of activity. There may be a

modulation of the circadian pattern of activity, persisting into subsequent cycles. There may be an entrainment response, reducing the likelihood that 24 hours later the animal again sees the light. In whatever way the animal accomplishes it, avoidance of light later on may enhance its fitness. So why should not light act as a US?

In this issue, de Groot and Rusak (2000) report their thorough but unsuccessful attempts to reproduce the results of Amir and Stewart. These obviously cast doubt on the generality of the previous findings. The present results should not be taken to mean that circadian organization has nothing to do with learning. The time is long past that endogenous circadian rhythms were themselves considered the product of learning. Pfeffer (1907) still viewed endogenous oscillations as “Nachschwingungen” or “after-oscillations,” induced by prior exposure to external periodicity. That notion was finally laid to rest when Aschoff showed in the 1950s that no prior exposure to an LD cycle was needed: Chickens raised from the egg in constant light (LL; Aschoff and Meyer-Lohmann, 1954), and mice raised even for seven generations in LL (Aschoff, 1955), still developed endogenous circadian rhythmicity. The phase-shifting response to light does not depend on learning either. It is right there, from the first millisecond flash of light hitting a *Drosophila* pupa. But the relationship between circadian rhythms and learning does not stop at the pacemaker and its response to light. There are three junctions where major research questions remain to be addressed. How does learning depend on circadian phase? Is the endogenous circadian behavioral program dependent on prior experience and learning? Can other entraining stimuli act via their prior association with light, which is the essence of the present debate?

CIRCADIAN PHASE DEPENDENCE OF LEARNING

Researchers have long been interested in the question of whether learning is affected by circadian phase. An impressive series of papers in the 1970s by Holloway and Wansley (e.g., 1973) demonstrated the complexity of this question. Earlier on, Leon Kamin (1957) had described the temporary suppression of retrieval of a learned passive avoidance task circa 6 h after training. 24 h after training, the information turned out to be fully present, and the performance on the task was just as good as 15 min after training. For nearly two decades, the "Kamin effect" was viewed as the main evidence for the transfer of information from short-term to long-term memory. What Holloway and Wansley showed was that the maximal performance recurs periodically in 24-h intervals after learning: The information is stored, but its use is suppressed at nonmultiples of 24 h. This suppression of performance is not present in rats with a complete lesion of the suprachiasmatic nucleus (Stephan and Kovacevic, 1978). The SCN apparently time-stamps the information: "not to be used at other times of day."

In the circadian field, we are used to the fact that nearly every aspect of behavior varies with phase of the circadian system. Acquisition and retrieval will each be affected by phase, even if only through the level of alertness and activity present at that phase. The phase difference between training and testing will also affect performance, as Holloway and Wansley showed. With repeated training on the same task, the intertraining interval plays a role. Stroebe (1967), for instance, found early on that conditioned emotional responses were acquired by rats much faster when they were trained repeatedly at the same time of day than when they were trained at random times. The rate of extinction was also faster when unreinforced tests were made at the same time of day. The complexity of the temporal dynamics of learning depending on multiple training and testing times rapidly becomes overwhelming and remains to be carefully sorted out. In addition to theoretical modeling, a precise and predictable learning response would be required to carry out this task. At this stage, the bottom line is that information may often be stored in a time-stamped manner and that in any learning study researchers should be aware of this source of variation. The role of the SCN seems to be to suppress the information at other than the training times of day.

The finding of a sudden expression of cholinergic receptors in the SCN 24 h after a single training only (Van der Zee et al., submitted) opens up an intriguing perspective on the potential neural substrate for this role of the SCN in learning.

IS THE CIRCADIAN BEHAVIORAL ROUTINE DUE TO LEARNING?

Time stamping clearly makes adaptive sense. The individual animal starting its day in a periodic world may do well to use its experience of yesterday as a template for today's behavior. The evidence that animals really do this is not overwhelming, and support for individual routines in nature is meager (e.g., Rijnsdorp et al., 1981). Chronobiology does not focus on details of behavior but on the underlying timing mechanism. That animals may incorporate time-stamped information is best documented in "time-place association" (TPA). The early work on TPA in honeybees (*Zeitgedächtnis*; Beling, 1929) is difficult to interpret because the food rewards used may have acted as zeitgebers, because honeybees communicate and because the place choice is not independent between individual workers in a hive. Better information is now available for songbirds. In an elegant series of papers, Biebach and co-workers showed that several Passerines are able to select feeding places at times of day when visits had been profitable on preceding days and that their circadian system is involved in these decisions (e.g., Biebach et al., 1991). The issue of adaptive modulation of circadian patterns is no doubt more complex than learning a sequence of food sources. Great tits exposed to unpredictable nocturnal temperatures learn to adjust their evening level of stored food reserves. They do so by an anticipatory rise in food intake around noon, in spite of the absence of any change in daytime conditions (Bednekoff et al., 1994). Thus, experience at one time of day may elicit adaptive behavioral adjustments at other times of day. Clearly, the involvement of the circadian system in the maintenance of "rheostatic" balance (Mrosovsky, 1990) is of a level of complexity that far exceeds the simple time stamping of experiences.

It is quite likely that human circadian physiology exploits similar strategies. Aschoff et al. (1974) observed that the body temperature of human subjects starts to rise even during sleep in anticipation of the time at which their sleep had been interrupted on

previous nights. There is evidently tremendous scope for research on how experience contributes to our own circadian routines.

CAN CIRCADIAN ENTRAINMENT BY OTHER CUES BE LEARNED?

The best known example of behavior elicited at a different circadian phase from that of the signal is "anticipatory activity." A few hours before the scheduled meal time, rats start a bout of intense voluntary activity; a second bout follows circa 12 h later (Aschoff, 1991). The scheduled meal serves both as a reinforcer and as an entraining agent. In the rat, it is not the central pacemaker in the SCN that is entrained, but a separate, food-entrainable oscillator (FEO): the SCN is not even required for the expression of the FEO (Stephan, 1982). That the FEO is truly entrained is demonstrated by the positive association of phase angle difference and the cycle length of the meal zeitgeber (Aschoff et al., 1983). In rats, the SCN may continue to free-run unaffected by the FEO, but in honeybees food entrainment of the pacemaker itself—possibly via feedback of an FEO onto the pacemaker—has been documented (Frisch and Aschoff, 1987). In rodents, such entraining feedback from activity onto the pacemaker is well-known (Mrosovsky, 1996).

In human circadian systems, both light and social signals (Aschoff et al., 1971) are potential zeitgebers. We know remarkably little about most customary social cues that might provide temporal information and replace light as a zeitgeber through a process of conditioning. What, for instance, is the influence of access to a wristwatch on the human circadian rhythm in an otherwise time-cue-free environment? What zeitgeber information is there in TV schedules? Can a favorite daily soap opera replace light as an entraining agent?

In the middle of the last century, chronobiology viewed circadian rhythms of animals and plants alike as a pretty diffuse property of the whole organism. In the 1970s, this view changed dramatically to one where the focus in zoology became one on discrete pacemakers in the CNS dictating their rhythm to the animal and mediating the entrainment by light. Recent molecular developments force us to amend the position again. Clearly, clock genes are expressed periodically in many tissues, and not always in phase with the central pacemaker (Yamazaki et al., 2000). In inter-

nal desynchronization, some tissues may be in synch with one of the rhythms, others with another. Although most tissues rely on the SCN (and light) for mutual coordination, they apparently do not all do so. Other external stimuli are probably exploited when needed, and the SCN, while providing the necessary access to light, also listens to other stimuli through internal mediators. Hence, the supposition that conditioning to a nonphotic signal could play a role in entrainment is not so far-fetched after all. The controversy in this issue over the rat's learning and entrainment response does not put an end to studies of the conditioning of circadian systems. It rather marks the beginning.

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